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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,971	AHOTUPA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *7-16,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 17-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8/14/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-20 are pending.

2. Claims 7-16 and 19-20 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 9/17/03, the following rejection remains.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-6 and 17-18 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of inhibiting oxidative burst in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are neutrophils, (2) a method of inhibiting myeloperoxidase activity in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are macrophages, and (3) a method of inhibiting Fas induced apoptosis in lymphocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, matairesino or enterolactone, and wherein the lymphocytes are T lymphocytes, **does not** reasonably provide enablement for (1) *any* method as set forth in claims 1-6 and 17-18 for treating *any* disease such as ischemia reperfusion injury wherein the injury is myocardial infraction, stroke, transplantation, adult respiratory distress syndrome, ischemic heart disease, enterotoxic or hemorrhagic shock, or any chronic condition such as rheumatoid arthritis, any allergic condition including asthma, any inflammatory condition such as inflammatory bowel disease or skin, HIV, AIDS, psoriasis, Parkinson's disease, Alzheimer's disease, any autoimmune disease such as type I or type II diabetes, hypercholesterolemic arteriosclerosis, cataract or amylotrophic lateral sclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only (1) a method of inhibiting oxidative burst in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are neutrophils, (2) a method of inhibiting myeloperoxidase activity in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are macrophages, and (3) a method of inhibiting Fas induced apoptosis in lymphocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, matairesino or enterolactone, and wherein the lymphocytes are T lymphocytes.

The specification does not teach how to use *any* lignan such as hydroxymatairesinol, matairesinol, enterolactone or a mixture thereof for inhibiting the overactivity of any phagocytes or lymphocytes in any individual for treating any disease because there is insufficient guidance as to the mixture of hydromatairesinol and matairesinol for inhibiting any overactivity of neutrophils such as oxidative burst. In fact the specification shows on page 9, Table 1 that the IC50 of matairesinol for oxidative burst is 11 and the IC50 of hydroxymatairesinol is 5.3 as compared to the 4-OH-toremifen, which is the inhibitor of oxidative burst that has an IC50 value of 1.7. The extent of inhibition by matairesinol is marginal at best. Further, there are no showing that the mixture of hydromatairesinol and matairesinol is effective for inhibiting any overactivity of neutrophils such as oxidative burst in vitro, much less in vivo, in turn, for treating any disease.

With regard to the method of inhibiting overactivity of phagocytes wherein the phagocytes are myeloid origin in an individual by administering to said individual any lignan wherein the lignan is matairesinol, or a mixture thereof of enterolactone and hydroxymatairesinol, the specification shows on page 9, Table 1 that the IC50 of matairesinol for myeloperoxidase activity is 44.5 and the IC50 of hydroxymatairesinol is 6.8 as compared to the Nitecapone, which is the inhibitor of myeloperoxidase activity, that has a IC50 value of 2.3. Based on these results,

it is not clear if Matairesinol could inhibit myeloperoxidase activity as claimed in the absence of a negative control. Further, there are no showings that the mixture of enterolactone and hydroxymatairesinol is effective for inhibiting any inhibiting overactivity of phagocytes that are myeloid origin such as myeloperoxidase activity in converting the reactive oxygen species released by any stimuli.

With regard to of inhibiting Fas induced apoptosis in T lymphocytes by administering an effective amount of a lignan in an individual wherein the lignan is hydroxymatairesinol, matairesino or enterolactone or "a mixture thereof", there are no vivo working example that administering to any individual *any* lignan mentioned above is effective for treating any disease.

Pool-Zobel *et al* teach that lignan such as enterolactone reduces oxidized bases at high, non-physiological concentrations but had no effects on oxidative stress (See page 1251, column 2, last paragraph, Fig 4 and 5, in particular).

A method of inhibiting overactivity of phagocytes or lymphocyte in an individual in the absence of in vivo data are unpredictable for the following reasons: (1) the lignan or lignans mentioned above may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the lignan; (2) the lignan may not reach the target area because, i.e. the lignan may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the lignan unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering any lignan such as hydroxymatairesinol, matairesino or enterolactone or a mixture thereof. The specification does not teach how to extrapolate data obtained from in vitro oxidative burst and myeloperoxidative assays to the development of a method of inhibiting "overeactivity of phagocytes or lymphocytes", commensurate in scope with the claimed invention.

The Merck manual does not recognize the use of *any* lignan such as hydroxymatairesinol, matairesino or enterolactone or a mixture thereof for inhibiting the overactivity of phagocytes or lymphocytes such as oxidative burst, myeloperoxidase activity, in turn, to treat, or to prevent any disease (See page 420-421, in particular). A person of skill in the art could not predict which particular lignan such as hydroxymatairesinol, matairesino or enterolactone or "a mixture thereof"

from which plant are effective for inhibiting overactivity of phagocytes or lymphocytes to treat or to prevent which disease. Even if the method is limited to in vitro, the specification discloses that not all lignans have the same properties such as inhibiting oxidative burst in neutrophils or inhibiting myeloperoxidase activity (See page 9, Table 1). Although some of the activities of lignans have been shown in vitro, the relevance of these studies to in vivo disease is not known. In view of the lack of guidance and the lack of predictability of structure-activity difference among three different lignans with respect to the specific oxidative burst, and myeloid peroxidase activity, much less to inhibiting overactivity of phagocytes or lymphocytes in vivo to treat or to prevent any disease, the lack of established clinical protocols for effective lignan based therapies for any disease such as such as ischemia reperfusion injury wherein the injury is myocardial infraction, stroke, transplantation, adult respiratory distress syndrome, ischemic heart disease, enterotoxic or hemorrhagic shock, or any chronic condition such as rheumatoid arthritis, any allergic condition including asthma, any inflammatory condition such as inflammatory bowel disease or skin, HIV, AIDS, psoriasis, Parkinson's disease, Alzheimer's disease, any autoimmune disease such as type I or type II diabetes, hypercholesterolemic arteriosclerosis, cataract or amylotrophic lateral sclerosis, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 9/17/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) there is a good predictability of in vivo effects of a drug once corresponding effects have been shown in vitro. (2) Applicant submits that articles by Dondona et al demonstrates that the drug carvedilol has antioxidative effects in humans in vivo (introduction, first paragraph). The same drug (Carvedilol) has been shown to possess

antioxidative properties, namely scavenging peroxy and hypochlorous radicals in chemical systems in vitro (reference number 3 in the listing at the end of the text). (3) The second reference, Davaraj et al submitted herewith, demonstrates that alpha tocopherol (Vitamin E) has antioxidative properties in humans in vivo. The agent decreases the release of reactive oxygen species, lipid oxidation, IL-1 secretion and monocyte adhesion to endothelium. (4) Enclosed is a copy of the Merck Manual index showing the structure of the two compounds. It can be seen that they are, like lignans, rather simple structures. Applicants thus respectively traverse the examiner's objection as to unpredictability between effects in vitro and in vivo. (5) The claims are directed to a method for inhibiting overactivity of phagocytes and lymphocytes. The claims are not directed to a method of treating any disease. (6) The

In response, the drug carvedilol and alpha tocophreol (vitamin E) are irrelevant to the claimed invention. Both Carvedilol and alpha tocophreol cited by Applicants do not have the same structure as the lignan recited in claim 1 for the claimed method of inhibiting *any* activity of phagocytes or lymphocytes in an individual such as human. The specification discloses only (1) a method of inhibiting oxidative burst in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are neutrophils, (2) a method of inhibiting myeloperoxidase activity in phagocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, and wherein the phagocytes are macrophages, and (3) a method of inhibiting Fas induced apoptosis in lymphocytes by administering an effective amount of a lignan *in vitro* wherein the lignan is hydroxymatairesinol, matairesino or enterolactone, and wherein the lymphocytes are T lymphocytes. The specification discloses that one of the objective of the claimed invention is "to decrease the formation of reactive oxygen species, caused by the overactive phagocytes (neutrophils), wherein said reactive oxygen species further could react with lipids, DNA or proteins and thereby cause diseases and disorders in the individual. The object is also to lower the risk, *prevent* or treat other diseases or conditions, which are not due to lipid, DNA or protein oxidation but which are due to overactive neutrophils. The specification further defines the conditions which can be treated or prevented by administering hydroxymatairesinol or matairesinol and which conditions result from this mechanism are acute ischemia-reperfusion injuries or chronic conditions such as myocardial infraction, stroke, transplantation, adult respiratory distress syndrome, ischemic heart disease, or endotoxic or hemmorhagic shock, chronic conditions such as rheumatoid arthritis, allergic conditions such as asthma, inflammatory

conditions such as inflammatory bowel disease or an inflammatory disease, HIV, MDS, psoriasis, Parkinson's disease, Alzheimer's disease, autoimmune diseases, type 1 or type 11 diabetes, hypercholesterolemic atherosclerosis, cataract or mylotrophic lateral sclerosis, type I and type II diabetes, type 1 and type 11 hypersensitivity reactions, a rejection reaction due to tissue transplantation, atherosclerosis and multiple sclerosis.

However, there is no showing in the specification as filed that the claimed method is effective in vivo for treating any disease mentioned above, let alone "preventing" any disease due to overactive neutrophils.

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

9. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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December 15, 2003

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